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A Pharmacokinetic Drug-Drug Interaction Study Between Raltegravir and Atorvastatin

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ABSTRACT

- **BACKGROUND**: Dyslipidemia is highly prevalent among patients with HIV infection and contributes to an increased risk of cardiovascular disease. Atorvastatin is a potent lipid-lowering agent and is used for prevention of cardiovascular disease. A complicating factor in the concomitant use of antiretroviral agents and statins is the occurrence of drug-drug interactions.This study was designed to investigate the influence of a frequently used statin, atorvastatin, on the pharmacokinetics of the HIV integrase inhibitor raltegravir and vice versa.
- **METHODOLOGY**: This was an open-label, cross-over, three-period phase I trial in 24 healthy volunteers. Subjects took raltegravir 400 mg BID for 7 days, atorvastatin 20 mg QD for 7 days, and the combination of atorvastatin 20 mg QD + raltegravir 400 mg BID for 7 days with 2-week washout periods in between. Treatment sequence was allocated at random. Intensive steady-state 12- and 24-hour pharmacokinetic (PK) blood sampling was performed on day 7 of each treatment period. PK parameters (AUC_{last}, C_{max}, C_{last}) were determined by non-compartmental analysis for raltegravir and the sum of atorvastatin and its active metabolites (atorvastatin-equivalents). Geometric mean ratios (GMR) of the test treatment [combination raltegravir + atorvastatin] versus the reference treatment [raltegravir or atorvastatin alone] and 90% confidence intervals (CI) were calculated after log-transformation of within-subject ratios. Fasting lipid profiles were obtained on day 1 and day 7 of each treatment period to assess short-term effect on serum low-density lipoprotein (LDL) cholesterol. To compare the change in LDL cholesterol after atorvastatin with and without raltegravir a paired t-test was performed.
- **RESULTS**: Twenty-four healthy volunteers, of which 11 males, were enrolled (23 Caucasian, 1 mixed race). One subject did not complete the treatment period with raltegravir alone due to reasons not related to the study. Median (range) age and BMI were 31 (18-55) years and 20.9 (18.3-28.9) kg/m^2, respectively. No serious adverse events were reported. GMR (90% CI) of raltegravir PK parameters were: 1.01 (0.68-1.51) for AUC_{0-12h}; 1.14 (0.70-1.86) for C_{max}; 0.96 (0.69-1.32) for C_{12h}. GMR (90% CI) of atorvastatin-equivalents PK parameters were: 0.98 (0.91-1.06) for AUC_{0-24h}; 1.02 (0.83-1.26) for C_{max}; 0.97 (0.87-1.10) for C_{24h}. Mean (95% CI) change in LDL cholesterol (day7 - day1) was -1.12 (-1.37;-0.87) mmol/L for atorvastatin alone compared to -1.29 (-1.50;-1.08) mmol/L for atorvastatin when combined with raltegravir (p=0.19).
- **CONCLUSIONS**: Co-administration of raltegravir and atorvastatin does not change the pharmacokinetics of either drug in a clinically meaningfull way. The combination can be safely administered without dose adjustments.

1. INTRODUCTION

- Dyslipidemia is highly prevalent among patients with HIV infection and contributes to an increased risk of cardiovascular disease, especially in patients ≥50 years of age.
- Atorvastatin is a potent lipid-lowering agent and is used for prevention of cardiovascular disease.
- A complicating factor in the concomitant use of antiretroviral agents and statins is the occurrence of drug-drug interactions.
- Raltegravir, an HIV-1 integrase inhibitor, does not influence CYP450 enzymes and has in general little propensity to interact with other medication.
- Therefore raltegravir could be one of the preferred antiretroviral agents in HIV-infected patients with dyslipidemia and statin-use, especially in older patients with other co-morbidities and subsequent use of co-medication.

2. OBJECTIVES

- To assess the effect of multiple dose atorvastatin on the steady state pharmacokinetics of raltegravir and vice versa by intrasubject comparison in healthy subjects.
- To evaluate the safety and tolerability of co-administration of raltegravir and atorvastatin in healthy subjects.
- To investigate the non-steady state changes in serum low density lipoprotein

3. METHODS

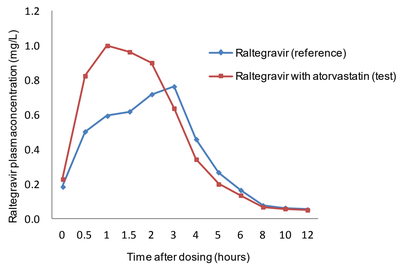
- An open-label, cross-over, three-period phase I trial in 24 healthy volunteers.
- Subjects took raltegravir 400 mg BID for 7 days, atorvastatin 20 mg QD for 7 days, and the combination of atorvastatin 20 mg QD + raltegravir 400 mg BID for 7 days with 2-week washout periods in between. Treatment sequence was allocated at random.
- Intensive steady-state pharmacokinetic (PK) blood sampling was performed on day 7 of each treatment period up to 12 hours (raltegravir) and 24 hours (atorvastatin) after observed intake of the study medication.
- PK parameters (AUC_{tau}, C_{max}, C_{last}, T_{max} and t_{half}) were determined by non-compartmental analysis for raltegravir and the sum of atorvastatin and its active metabolites atorvastatin lactone, o-hydroxyatorvastatin and p-hydroxyatorvastatin (atorvastatin-equivalents).
- Geometric mean ratios (GMRs) of the PK parameters of the test treatment [combination raltegravir + atorvastatin] versus the reference treatment [raltegravir or atorvastatin alone] and 90% confidence intervals (CI) were calculated after log-transformation of within-subject ratios (Phoenix version 6.3.).
- Safety assessments were performed throughout the study.
- Fasting lipid profiles were obtained on day 1 and day 7 of each treatment period.
- To compare the change from baseline (day 1) in LDL cholesterol after atorvastatin use with and without raltegravir a paired t-test was performed (IBM SPSS statistics 20).
- This trial is registered at ClinicalTrials.gov, number NCT01779687.

4. RESULTS

- Twenty-four healthy volunteers, of which 11 males and 13 females, were included in the study (23 Caucasian, 1 mixed race). One subject did not complete the treatment period with raltegravir alone due to reasons not related to the study.
- Mean (range) age and Body Mass Index were 31 (18-55) years and 20.9 (18.3-28.9) kg/m^2, respectively.

Pharmacokinetics

Figure 1: Raltegravir mean plasma concentrations vs. time curves



4. RESULTS (continued)

- The steady-state PK of raltegravir in the presence and absence of atorvastatin are shown in Figure 1 and Table 1.
- It is well known that the pharmacokinetics of raltegravir displays large intersubject variability, which was observed in our study as well. The GMR of the exposure to raltegravir (AUC_{0-12h}) is close to 1.0. The large 90% confidence interval for the GMR partly overlaps the predefined range of 0.74 to 1.35 and reflects the variability in the individual changes in the AUC_{0-12h} (see Figure 3).

Table 1: Pharmacokinetic parameters raltegravir

	RAL alone		RAL + ATOR		RAL+ATOR/RAL alone	
	Geometric mean	95% CI	Geometric mean	95% CI	GMR	90% CI
AUC_{0-12h} (h*mg/L)	4.13	(2.90-5.87)	4.23	(2.92-6.13)	1.01	(0.68-1.51)
C_{max} (mg/L)	1.29	(0.83-1.99)	1.48	(0.96-2.28)	1.14	(0.70-1.86)
T_{max} (h)*	1.5	(0-12)	1.5	(0-4)		
C_{12h} (mg/L)	0.052	(0.035-0.077)	0.049	(0.039-0.062)	0.96	(0.69-1.32)
t_{half} (h)	3.40	(2.80-4.12)	3.94	(3.24-4.81)	1.15	(0.92-1.44)

* T_{max}: median (min-max)
RAL = raltegravir; ATOR = atorvastatin

- The steady-state pharmacokinetics of atorvastatin-equivalents in the presence and absence of raltegravir are displayed in Figure 2 + 3 and Table 2.
- The GMR of the exposure to atorvastatin-equivalents (AUC_{0-24h}) is close to 1.0. The 90% CI falls entirely within the range of 0.80 to 1.25 which is considered to indicate no significant interaction.

Figure 2: Atorvastatin mean plasma concentrations vs. time curves

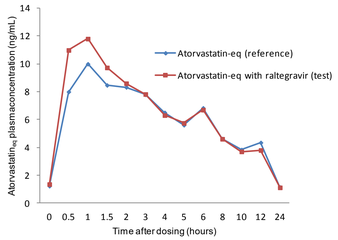


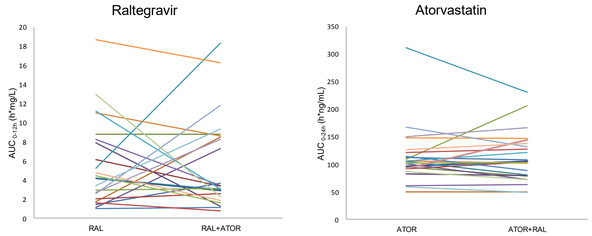
Table 2: Pharmacokinetic parameters atorvastatin equivalents

	ATOR alone		ATOR + RAL		ATOR + RAL / ATOR alone	
	Geometric mean	95% CI	Geometric mean	95% CI	GMR	90% CI
AUC_{0-24h} (h*ng/mL)	104.0	(89.1-121.4)	102.3	(86.5-121.1)	0.98	(0.91-1.06)
C_{max} (ng/mL)	15.79	(12.55-19.86)	16.12	(12.92-20.10)	1.02	(0.83-1.26)
T_{max} (h) *	0.75	(0.5-6)	0.5	(0.5-2)		
C_{24h} (ng/mL)	1.15	(0.99-1.33)	1.12	(0.95-1.32)	0.97	(0.87-1.10)
t_{half} (h)	7.88	(7.22-8.59)	7.87	(7.10-8.73)	1.00	(0.91-1.09)

* T_{max}: median (min-max)
RAL = raltegravir; ATOR= atorvastatin

4. RESULTS (continued)

Figure 3 Individual AUC_{0-tau} values raltegravir and atorvastatin



Safety

- No serious adverse events (SAEs) were reported.
- In total 30 AEs (25% of the total number of AEs reported) were considered possibly (n=23) of probably (n=7) drug-related .
- Most frequently reported possibly and probably drug-related AEs were myalgia (n=6; 4 subjects), elevated creatine kinase (CK) (n=6), abdominal pain (n=4), fatigue (n=3), headache (n=2) and nausea (n=2). All these AEs were mild (toxicity grade 1 and 2), transient and were not related to a specific treatment period.

Table 3: Lipid-lowering effects atorvastatin

Treatment	Mean change LDL cholesterol (mmol/L)	95% CI	p-value
Atorvastatine alone	-1.12	(-1.37; -0.87)	0.19
Atorvastatine with raltegravir	-1.29	(-1.50;-1.08)	

- Mean change in LDL cholesterol (day7 - day1) for atorvastatin alone compared to atorvastatin when combined with raltegravir is not significantly different.

5. CONCLUSIONS

- Co-administration of raltegravir and atorvastatin does not change the pharmacokinetics of either drug in a clinically meaningfull way.
- Raltegravir does not influence the short-term lipid-lowering effect of atorvastatin.
- The combination can be safely administered without dose adjustments.

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